CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 20-058/S-010

Trade Name: Thioplex® for Injection

Generic Name: thiotepa

Sponsor: Immunex Corporation

Approval Date: October 12, 2000

CENTER FOR DRUG EVALUATION AND RESEARCH

NDA 20-058/S-010

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-058/S-010

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-058/S-009 and S-010

Immunex Corporation
51 University Street
Seattle, WA 98101-2936

OCT 12 2000

Attention: Mark Gauthier, Senior Manager
Regulatory Affairs

Dear Mr. Gauthier:

Please refer to your supplemental new drug applications described below and submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Thioplex® (thiotepa) for Injection.

We also refer to your amendment of August 30, 2000.

These supplemental new drug applications provide for:

S-009 Submitted January 21, 2000 and received January 24, 2000. Revisions to the package insert to include geriatric labeling to the PRECAUTIONS section.

S-010 Submitted June 8, 2000 and received June 12, 2000. A new formulation containing sodium carbonate.

We have completed the review of these supplemental applications, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon labeling text. Accordingly, the supplemental applications are approved effective on the date of this letter.

Please note that your request for extension of expiry to 24 months is also approved.

The final printed labeling (FPL) must be identical to the submitted labeling (text for the package insert submitted June 8, 2000). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and unapproved new drug.

Please submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. Alternatively, you may submit the FPL electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDAs* (January 1999). For administrative purposes, this submission should be designated "FPL for approved supplement NDA 20-058/S-010." Approval of this submission by FDA is not required before the labeling is used.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Practitioner" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Patty Garvey, Project Manager, at 301-594-5766.

Sincerely,

R Pazdur 10/4/00

Richard Pazdur, M.D.
Director
Division of Oncology Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

cc:
Archival NDA 20-058
HFD-150/Div. Files
HFD-150/png
HFD-150/NChidambaram/Eduffy – 10/5/00
HF-2/MedWatch (with labeling)
HFD-002/ORM (with labeling)
HFD-101/ADRA (with labeling)
HFD-42/DDMAC (with labeling)
HFI-20/Press Office (with labeling)
HFD-400/OPDRA (with labeling)
HFD-613/OGD (with labeling)
HFD-21/ACS (with labeling) - ONLY for drug discussed at advisory committee meeting.
HFD-095/DDMS-IMT
HFD-093/DDMS-IST (with labeling)
HFD-810/JSimmons
DISTRICT OFFICE

Drafted by: png/10-3-2000
Initialed by: DPease/ 10-5-00
NCh2/10-5-00
Final by:png/10-6-2000
filename: C:\My Documents\Immunex\N20058\Letters\AP_S09.010.1000.doc

APPROVAL (AP) - S009
APPROVAL (AP) - S010

DPease
10-12-00

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-058/S-010

LABELING

CI 6329-1

THIOPLEX®

Thiotepa For Injection

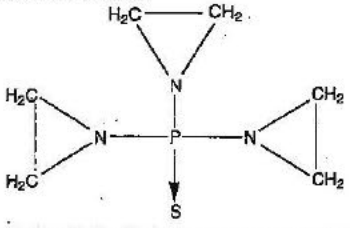
15 mg/Vial

Rx only

DESCRIPTION

THIOPLEX® (thiotepa for injection) is an ethylenimine-type compound. It is supplied as a non-pyrogenic, sterile lyophilized powder for intravenous, intracavitary or intravesical administration, containing 15 mg of thiotepa and 0.03 mg/vial (0.2%) of sodium carbonate. THIOPLEX is a synthetic product with antitumor activity. The chemical name for thiotepa is Aziridine, 1,1',1''-phosphinothioylidynetris-, or Tris (1-aziridinyl) phosphine sulfide.

Thiotepa has the following structural formula:



Thiotepa has the empirical formula $C_6H_{12}N_3PS$ and a molecular weight of 189.22. When reconstituted with Sterile Water for Injection, the resulting solution has a pH of approximately 6.5 - 8.1. Thiotepa is stable in alkaline medium and unstable in acid medium.

CLINICAL PHARMACOLOGY

Thiotepa is a cytotoxic agent of the polyfunctional type, related chemically and pharmacologically to nitrogen mustard. The radiomimetic action of thiotepa is believed to occur through the release of ethylenimine radicals which, like irradiation, disrupt the bonds of DNA. One of the principal bond disruptions is initiated by alkylation of guanine at the N-7 position, which severs the linkage between the purine base and the sugar and liberates alkylated guaninae.

The pharmacokinetics of thiotepa and TEPA in thirteen female patients (45 - 84 years) with advanced stage ovarian cancer receiving 60 mg and 80 mg thiotepa by intravenous infusion on subsequent courses given at 4-week intervals are presented in the following table:

	Mean ± SEM			
Pharmacokinetic Parameters	Thiotepa		TEPA	
(units)	60 mg	80 mg	60 mg	80 mg
Peak Serum concentration (ng/mL)	1331 ± 119	1828 ± 135	273 ± 46	353 ± 46
Elimination half-life (h)	2.4 ± 0.3	2.3 ± 0.3	17.6 ± 3.6	15.7 ± 2.7
Area under the curve (ng/h/mL)	2832 ± 412	4127 ± 666	4789 ± 1022	7452 ± 1667
Total body clearance (mL/min)	446 ± 63	419 ± 56		

TEPA, which possesses cytotoxic activity, appears to be the major metabolite of thiotepa found in human serum and urine. Urinary excretion of ^{14}C-labeled thiotepa and metabolites in a 34-year old patient with metastatic carcinoma of the cecum who received a dose of 0.3 mg/kg intravenously was 83%. Thiotepa and TEPA in urine each accounts for less than 2% of the administered dose.

The pharmacokinetics of thiotepa in renal and hepatic dysfunction patients have not been evaluated. Possible pharmacokinetic interactions of thiotepa with any concomitantly administered medications have not been formally investigated.

INDICATIONS AND USAGE

Thiotepa has been tried with varying results in the palliation of a wide variety of neoplastic diseases. However, the most consistent results have been seen in the following tumors:

1. Adenocarcinoma of the breast.
2. Adenocarcinoma of the ovary.
3. For controlling intracavitary effusions secondary to diffuse or localized neoplastic diseases of various serosal cavities.
4. For the treatment of superficial papillary carcinoma of the urinary bladder.

While now largely superseded by other treatments, thiotepa has been effective against other lymphomas, such as lymphosarcoma and Hodgkin's disease.

CONTRAINDICATIONS

THIOPLEX is contraindicated in patients with a known hypersensitivity (allergy) to this preparation.

Therapy is probably contraindicated in cases of existing hepatic, renal, or bone-marrow damage. However, if the need outweighs the risk in such patients, thiotepa may be used in low dosage, and accompanied by hepatic, renal and hemopoietic function tests.

WARNINGS

Death has occurred after intravesical administration, caused by bone-marrow depression from systematically absorbed drug.

Death from septicemia and hemorrhage has occurred as a direct result of hemetopoietic depression by thiotepa.

Thiotepa is highly toxic to the hematopoietic system. A rapidly falling white blood cell or platelet count indicates the necessity for discontinuing or reducing the dosage of thiotepa. Weekly blood and platelet counts are recommended during therapy and for at least 3 weeks after therapy has been discontinued.

Thiotepa can cause fetal harm when administered to a pregnant woman. Thiotepa given by the intraperitoneal (IP) route was teratogenic in mice at doses ≥1 mg/kg (3.2 mg/m²), approximately 8-fold less than the maximum recommended human therapeutic dose (0.6 mg/kg, 27 mg/m²), based on body-surface area. Thiotepa given by the IP route was teratogenic in rats at doses ≥3 mg/kg (21 mg/m²), approximately equal to the maximum recommended human therapeutic dose, based on body-surface area. Thiotepa was lethal to rabbit fetuses at a dose of 3 mg/kg (41 mg/m²), approximately two times the maximum recommended human therapeutic dose based on body-surface area.

Effective contraception should be used during thiotepa therapy if either the patient or partner is of childbearing potential. There are no adequate and well-controlled studies in pregnant women. If thiotepa is used during pregnancy, or if pregnancy occurs during thiotepa therapy, the patient and partner should be apprised of the potential hazard to the fetus.

Thiotepa is a polyfunctional alkylating agent, capable of cross-linking the DNA within a cell and changing its nature. The replication of the cell is, therefore, altered, and thiotepa may be described as mutagenic. *An in vitro* study has shown that it causes chromosomal aberrations of the chromatid type and that the frequency of induced aberrations increases with the age of the subject.

Like many alkylating agents, thiotepa has been reported to be carcinogenic when administered to laboratory animals. Carcinogenicity is shown most clearly in studies using mice, but there is some evidence of carcinogenicity in man. In patients treated with thiotepa, cases of myelodysplastic syndromes and acute non-lymphocytic leukemia have been reported.

PRECAUTIONS

General

The serious complication of excessive thiotepa therapy, or sensitivity to the effects of thiotepa, is bone-marrow depression. If proper precautions are not observed thiotepa may cause leukopenia, thrombocytopenia, and anemia.

Information for Patients

The patient should notify the physician in the case of any sign of bleeding (epistaxis, easy bruising, change in color of urine, black stool) or infection (fever, chills) or for possible pregnancy to patient or partner.

Effective contraception should be used during thiotepa therapy if either the patient or the partner is of childbearing potential.

Laboratory Tests

The most reliable guide to thiotepa toxicity is the white blood cell count. If this falls to 3000 or less, the dose should be discontinued. Another good index of thiotepa toxicity is the platelet count; if this falls to 150,000, therapy should be discontinued. Red blood cell count is a less accurate indicator of thiotepa toxicity. If the drug is used in patients with hepatic or renal damage (see **CONTRAINDICATIONS** section), regular assessment of hepatic and renal function tests are indicated.

Drug Interactions

It is not advisable to combine, simultaneously or sequentially, cancer chemotherapeutic agents or a cancer chemotherapeutic agent and a therapeutic modality having the same mechanism of action. Therefore, thiotepa combined with other alkylating agents such as nitrogen mustard or cyclophosphamide or thiotepa combined with irradiation would serve to intensify toxicity rather than to enhance therapeutic response. If these agents must follow each other, it is important that recovery from the first agent, as indicated by white blood cell count, be complete before therapy with the second agent is instituted.

Other drugs which are known to produce bone-marrow depression should be avoided.

Carcinogenesis, Mutagenesis and Impairment of Fertility

Also see **WARNINGS** section.

Carcinogenesis

In mice, repeated IP administration of thiotepa (1.15 or 2.3 mg/kg three times per week for 52 or 43 weeks, respectively) produced a significant increase in the combined incidence of squamous-cell carcinomas of the skin, preputial gland, and ear canal, and combined incidence of lymphoma and lymphocytic leukemia. In other studies in mice, repeated IP administration of thiotepa (4 or 8 mg/kg three times per week for 4 weeks followed by a 20-week observation period or 1.6 mg/kg three times per week for 4 weeks followed by a 35-week observation period) resulted in an increased incidence of lung tumors. In rats, repeated IP administration of thiotepa (0.7 or 1.4 mg/kg three times per week for 52 or 34 weeks, respectively) produced significant increases in the incidence of squamous-cell carcinomas of the skin or ear canal, combined hematopoietic neoplasms, and uterine adenocarcinomas. Thiotepa given intravenously (IV) to rats (1 mg/kg once per week for 52 weeks) produced an increased incidence of malignant tumors (abdominal cavity sarcoma, lymphosarcoma, myelosis, seminoma, fibrosarcoma, salivary gland hemangioendothelioma, mammary sarcoma, pheochromocytoma) and benign tumors.

The lowest reported carcinogenic dose in mice (1.15 mg/kg, 3.68 mg/m²) is approximately 7-fold less than the maximum recommended human therapeutic dose based on body-surface area. The lowest reported carcinogenic dose in rats (0.7 mg/kg, 4.9 mg/m²) is approximately 6-fold less than the maximum recommended human therapeutic dose based on body-surface area.

Mutagenesis

Thiotepa was mutagenic *in in vitro* assays in *Salmonella typhimurium*, *E. coli*, Chinese hamster lung and human lymphocytes. Chromosomal aberrations and sister chromatid exchanges were observed *in vitro* with thiotepa in bean root tips, human lymphocytes, Chinese hamster lung, and monkey lymphocytes. Mutations were observed with oral thiotepa in mice at doses >2.5 mg/kg (8 mg/m²). The mouse micronucleus test was positive with IP administration of >1 mg/kg (3.2 mg/m²). Other positive *in vivo* chromosomal aberration or mutation assays included *Drosophila melanogaster*, Chinese hamster marrow, murine marrow, monkey lymphocyte, and murine germ cell.

Impairment of Fertility

Thiotepa impaired fertility in male mice at PO or IP doses ≥0.7 mg/kg (2.24 mg/m²), approximately 12-fold less than the maximum recommended human therapeutic dose based on body-surface area. Thiotepa (0.5 mg) inhibited implantation in female rats when instilled into the uterine cavity. Thiotepa interfered with spermatogenesis in mice at IP doses ≥0.5 mg/kg (1.6 mg/m²), approximately 17-fold less than the maximum recommended human therapeutic dose based on body-surface area. Thiotepa interfered with spermatogenesis in hamsters at an IP dose of 1 mg/kg (4.1 mg/m²), approximately 7-fold less than the maximum recommended human therapeutic dose based on body-surface area.

Pregnancy

Category D: See **WARNINGS** section.

Thiotepa can cause fetal harm when administered to a pregnant woman. Thiotepa given by the IP route was teratogenic in mice at doses ≥1 mg/kg (3.2 mg/m²), approximately 8-fold less than the maximum recommended human therapeutic dose based on body-surface area. Thiotepa given by the IP route was teratogenic in rats at doses ≥3 mg/kg (21 mg/m²), approximately equal to the max-

imum recommended human therapeutic dose based on body-surface area. Thiotepa was lethal to rabbit fetuses at a dose of 3 mg/kg (4.1 mg/m²), approximately 2 times the maximum recommended human therapeutic dose based on body-surface area. Patients of childbearing potential should be advised to avoid pregnancy. There are no adequate and well-controlled studies in pregnant women. If thiotepa is used during pregnancy, or if pregnancy occurs during thiotepa therapy, the patient and partner should be apprised of the potential hazard to the fetus.

Nursing Mothers

It is not known whether thiotepa is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for tumorigenicity shown for thiotepa in animal studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

Clinical studies of thiotepa did not include sufficient numbers of subjects aged 65 and over to determine whether elderly subjects respond differently from younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreasing hepatic, renal or cardiac function, and of concomitant disease or other drug therapy.

ADVERSE REACTIONS

In addition to its effect on the blood-forming elements (see **WARNINGS** and **PRECAUTIONS** sections), thiotepa may cause other adverse reactions.

General: Fatigue, weakness. Febrile reaction and discharge from a subcutaneous lesion may occur as the result of breakdown of tumor tissue.

Hypersensitivity Reactions: Allergic reactions - rash, urticaria, laryngeal edema, asthma, anaphylactic shock, wheezing.

Local Reactions: Contact dermatitis, pain at the injection site.

Gastrointestinal: Nausea, vomiting, abdominal pain, anorexia.

Renal: Dysuria, urinary retention. There have been rare reports of chemical cystitis or hemorrhagic cystitis following intravesical, but not parenteral administration of thiotepa.

Respiratory: Prolonged apnea has been reported when succinylcholine was administered prior to surgery, following combined use of thiotepa and other anticancer agents. It was theorized that this was caused by decrease of pseudocholinesterase activity caused by the anticancer drugs.

Neurologic: Dizziness, headache, blurred vision.

Skin: Dermatitis, alopecia. Skin depigmentation has been reported following topical use.

Special Senses: Conjunctivitis.

Reproductive: Amenorrhea, interference with spermatogenesis.

OVERDOSAGE

Hematopoietic toxicity can occur following overdose, manifested by a decrease in the white cell count and/or platelets. Red blood cell count is a less accurate indicator of thiotepa toxicity. Bleeding manifestations may develop. The patient may become more vulnerable to infection, and less able to combat such infection.

Dosages within and minimally above the recommended therapeutic doses have been associated with potentially life-threatening hematopoietic toxicity. Thiotepa has a toxic effect on the hematopoietic system that is dose related.

Thiotepa is dialyzable.

There is no known antidote for overdosage with thiotepa. Transfusions of whole blood or platelets have proven beneficial to the patient in combating hematopoietic toxicity.

DOSAGE AND ADMINISTRATION

Since absorption from the gastrointestinal tract is variable, thiotepa should not be administered orally.

Dosage must be carefully individualized. A slow response to thiotepa does not necessarily indicate a lack of effect. Therefore, increasing the frequency of dosing may only increase toxicity. After maximum benefit is obtained by initial therapy, it is necessary to continue the patient on maintenance therapy (1 to 4 week intervals). In order to continue optimal effect, maintenance doses should not be administered more frequently than weekly in order to preserve correlation between dose and blood counts.

Preparation and Administration Precautions: Thiotepa is a cytotoxic anticancer drug and as with other potentially toxic compounds, caution should be exercised in handling and preparation of thiotepa. Skin reactions associated with accidental exposure to thiotepa may occur. The use of gloves is recommended. If thiotepa solution contacts the skin, immediately wash the skin thoroughly with soap and water. If thiotepa contacts mucous membranes, the membranes should be flushed thoroughly with water.

Preparation of Solution: THIOPLEX (thiotepa for injection) should be reconstituted with 1.5 mL of Sterile Water for Injection resulting in a drug concentration of approximately 10 mg/mL. The actual withdrawable quantities and concentration achieved are illustrated in the following table:

Label Claim (mg/vial)	Actual Content (mg/vial)	Amount of Diluent to be Added (mL)	Approximate Withdrawable Volume (mL)	Approximate Withdrawable Amount (mg/vial)	Approximate Reconstituted Concentration (mg/mL)
15.0	15.6	1.5	1.4	14.7	10.4

The reconstituted solution is hypotonic and should be further diluted with Sodium Chloride Injection (0.9% sodium chloride) before use.

When reconstituted with Sterile Water for Injection, solutions of THIOPLEX should be stored in a refrigerator and used within 8 hours. Reconstituted solutions further diluted with Sodium Chloride Injection should be used immediately.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Initial and Maintenance Doses: Initially the higher dose in the given range is commonly administered. The maintenance dose should be adjusted weekly on the basis of pretreatment control blood counts and subsequent blood counts.

Intravenous Administration: Thiotepa may be given by rapid intravenous administration in doses of 0.3 to 0.4 mg/kg. Doses should be given at 1 to 4 week intervals.

Intracavitary Administration: The dosage recommended is 0.6 - 0.8 mg/kg. Administration is usually effected through the same tubing which is used to remove the fluid from the cavity involved.

Intravesical Administration: Patients with papillary carcinoma of the bladder are dehydrated for 8 to 12 hours prior to treatment. Then 60 mg of thiotepa in 30 - 60 mL of Sodium Chloride Injection is instilled into the bladder by catheter. For maximum effect, the solution should be retained for 2 hours. If the patient finds it impossible to retain 60 mL for 2 hours, the dose may be given in a volume of 30 mL. If desired, the patient may be positioned every 15 minutes for maximum area contact. The usual course of treatment is once a week for 4 weeks. The course may be repeated if necessary, but second and third courses must be given with caution since bone-marrow depression may be increased. Deaths have occurred after intravesical administration, caused by bone-marrow depression from systemically absorbed drug.

Handling and Disposal: Follow safe cytotoxic agent handling procedures. Several guidelines on this subject have been published.[1-6] There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

HOW SUPPLIED

THIOPLEX® (thiotepa for injection), for single use only, is available in vials containing 15 mg of non-pyrogenic, sterile lyophilized powder, supplied as follows:

NDC 58406-682-38 - 6 x 15 mg/vial

STORAGE

Store in refrigerator between 2-8°C (36-46°F). PROTECT FROM LIGHT AT ALL TIMES.

REFERENCES

1. Recommendations for the Safe Handling of Parenteral Antineoplastic Drugs. NIH Publication No. 83-2621. For sale by the Superintendent of Documents, US Government Printing Office, Washington, DC 20402.
2. AMA Council Report. Guidelines for Handling Parenteral Antineoplastics, *JAMA*. 1985; 253(11):1590-1592.
3. National Study Commission on Cytotoxic Exposure - Recommendations for Handling Cytotoxic Agents. Available from Louis P. Jeffrey, Sc D, Chairman, National Study Commission on Cytotoxic Exposure, Massachusetts College of Pharmacy and Allied Health Sciences, 179 Longwood Avenue, Boston, Massachusetts 02115.
4. Clinical Oncological Society of Australia: Guidelines and recommendations for safe handling of antineoplastic agents. *Med J Australia*. 1983; 1:426-428.
5. Jones RB, et al. Safe handling of chemotherapeutic agents: A report from the Mount Sinai Medical Center. Ca - *A Cancer Journal for Clinicians*. Sept/Oct 1983; 258-263.
6. American Society of Hospital Pharmacists technical assistance bulletin on handling cytotoxic and hazardous drugs. *Am J Hosp Pharm*. 1990; 47:1033-1049.

immunex®

Manufactured for IMMUNEX CORPORATION, Seattle, WA 98101
by LEDERLE PARENTERALS, INC., Carolina, Puerto Rico 00987

Rev 0378-00
Revised 10/2000

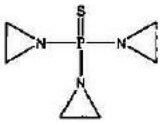
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-058/S-010

CHEMISTRY REVIEW(S)

OCT - 5 2000

CHEMIST'S REVIEW #1	1. ORGANIZATION HFD-150 DODP	2. NDA NUMBER 20-058	
3. NAME AND ADDRESS OF APPLICANT (City and State) Imuunex Corporation 51 University Street Seattle, Washington 98101-2936.		4. AF NUMBER	
		5. SUPPLEMENT (S) NUMBER(S) DATES(S)	
6. NAME OF DRUG Thioplex	7. NONPROPRIETARY NAME Thiotepa for Injection	SCF-010	06-12-2000
8. SUPPLEMENT PROVIDES FOR: Sodium Carbonate adjusted formulation.		9. AMENDMENTS DATES SCF-010 BC, 08-31-2000	
10. PHARMACOLOGICAL CATEGORY Anti-neoplastic	11. HOW DISPENSED RX ☐ OTC ____	12. RELATED ~~IND/NDA~~/DMF	
13. DOSAGE FORM(S) Lyophilized powder	14. POTENCY 15 mg/vial	DMF # (b) (4) (b) (4)	
15. CHEMICAL NAME AND STRUCTURE Aziridine, 1,1',1''-phosphinothioylidynetris-. Tris(1-aziridinyl)phosphine sulfide $C_6H_{12}N_3PS$, MW = 189.21 		16. RECORDS AND REPORTS CURRENT YES ☐ NO ____ REVIEWED YES ☐ NO ____	
17. COMMENTS Please see the review notes.			
18. CONCLUSIONS AND RECOMMENDATIONS Approval is recommended. "The applicant's request for an extension of expiry dating period to 24 months is also granted".			
19. REVIEWER			
NAME Nallaperumal Chidambaram, Ph.D.	SIGNATURE		DATE COMPLETED 10-05-2000

DISTRIBUTION DNDC 1 Div. Directors	ORIGINAL NDA	DIVISION FILE	Reviewer: N. Chidambaram HFD-150	CSO: D. Pease HFD-150	Chemistry Team Leader: E. Duffy HFD-150

Eric P. Duffy
10/5/00

Following this page, 4 Pages Withheld in Full as (b)(4)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-058/S-010

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

SEP 25 2000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

N 20-058/ S-010 **Submission Dates**: June 08, 2000

Drug Name, Dose, and Formulation: THIOPLEX®, 15 mg/vial, sterile lyophilized powder.
Sponsor: Immunex Corporation, Seattle, WA 98101
Reviewer: N.A.M. Atiqur Rahman
Type of Submission: Supplemental NDA

The review grants a waiver of the requirements for bioequivalence and bioavailability data as specified in 21 CFR 320.22(b)(1)(i) for the reformulated THIOPLEX® injection. The drug product includes 0.03 mg of sodium carbonate per vial, [redacted] (b) (4) Addition of sodium bicarbonate is [redacted] (b) (4) Please see attachment for the proposed new formulation.

RECOMMENDATION

The applicant's request of a biowaiver for the reformulated THIOPLEX® injection is granted.

N.A.M. Atiqur Rahman 9/11/00

N.A.M. Atiqur Rahman, Ph.D.
Team Leader, Oncology
DPE1, OCPB

C Sahajwalla 9/25/00

Chandra Sahajwalla, Ph.D.
Deputy Director, DPE1
OCPB

cc: NDA 20-058 (orig),
HFD-150 Division File
HFD-150 HFD-150, PGarvey, EDuffy, NChidambaram
HFD-150 JJohnson
HFD-860 MMehta, CSahajwalla, ARahman
CDR BMurphy

ATTACHMENT

Immunex Corporation
THIOPLEX
Supplement to NDA- 20-058

1. DRUG PRODUCT

Section B. Composition of THIOPLEXO Sodium Carbonate Adjusted Formula

This supplemental application provides for the addition of 0.03 mg of sodium carbonate (Na2C03) per vial (b) (4) of THIOPLEX® (Thiotepa for Injection), USP, 15 mg per vial, (b) (4) (b) (4) The proposed formulation modification (b) (4) for THIOPLEX®. Except for the proposed addition of sodium carbonate, (b) (4)

This section contains a revised product Composition Table for the THIOPLEX® (Thiotepa for Injection), USP, 15 mg per vial new formulation.

Immunex Corporation
THIOPLEX
Supplement to NDA- 20-058

Composition Table of THIOPLEXO Sodium Carbonate

Ingredients: Thiotepa, USP
Sodium Carbonate [redacted] (Na2C03)
[redacted]

Quantitative composition of THIOPLEX® (Thiotepa for Injection), USP, 15 mg per vial:

Ingredients	Reference	Role	mg per mL	Quantity/ Production [redacted] Batch	Unit Dosage Strength mg/vial
Thiotepa	USP	Active	20	[redacted]	[redacted]
Na2CO3	NF	[redacted]	0.03 [redacted]		
[redacted]					

[redacted]

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-058/S-010

OTHER REVIEW(S)

PROJECT MANAGER REVIEW OF LABELING

NDA 20-058/S-010 OCT 1 2 2000

Drug: THIOPLEX® (Thiotepa) for Injection, USP

Applicant: Immunex Corporation

Submission Date (s): June 6, 2000 **Receipt Date(s): June 12, 2000**

BACKGROUND:

This supplement is submitted as a prior approval supplement and proposes revisions to the DESCRIPTION and HOW SUPPLIED, as a result of applicant's sodium carbonate adjusted formula.

The sponsor has provided draft labeling to include the addition of sodium carbonate.

DOCUMENT REVIEWED:

This proposed draft labeling was compared to the latest approved FPL in supplement 004 approved on November 26, 1997.

REVIEW:

In comparing the above-identified FPLs to the currently proposed draft, I found the following changes:

1. The amount of Sodium Carbonate "and 0.03 mg/vial (0.2%) of Sodium Carbonate" was added to the Description section.

   This revision is acceptable.

2. The resulting solution pH was changed from approximately 5.5 – 7.5 to "6.5 – 8.1" in the Description section.

   This revision is acceptable.

3. The NDC number was changed from 58406-661-31 to "58406-662-36" in the How Supplied section.

   This revision is acceptable.

4. A "Geriatric Use" subsection has been added per S009 (submitted January 21, 2000 as a CBE), using the standard wording from 21 CFR 201.57(f)(10)(ii)(A). See separate review for S009.

CONCLUSION – RECOMMENDED REGULATORY ACTION:

With the concurrence of the chemist, this supplement should be approved and FPL requested to be submitted.

10/6/2000
Patty Garvey, R.Ph.
Project Manager

10-5-00
Dotti Pease
Chief, Project Manager

10/05/2000
Nallaperum Chidambaram, Ph.D.
Chemist

cc: Orig. NDA 20-058
HFD-150/ Div. File
HFD-150/PGarvey/Dpease/NChidambaram
HFD-2/Medwatch
HFD-150/png/drafted 10-3-00/date final typed

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-058/S-010

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO: *(Division/Office)* Dr. Atiq Rahman HFD-860 ioPharm Team Leader	FROM: Oncology Drug Products HFD-150

DATE	IND NO.	NDA No. 20-058	TYPE OF DOCUMENT	DATE OF DOCUMENT
07/20/2000			Supplement SCF - 010	06.08.2000

NAME OF DRUG(S)	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Thioplex (Thiotepa for Injection)		ANTINEOPLASTIC	Before 10.12.2000

NAME OF FIRM : Immunex

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY _____
- ☐ PRE-NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(Specify below)*

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER	☐ CHEMISTRY ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☒ BIOAVAILABLITY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ *IN-VIVO* MAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS *(List below)*
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

☒ CLINICAL ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS *(Attach additional sheets if necessary)*
This is a formulation change supplement. In the new formulation, the applicant has added sodium carbonate (b) (4) (b) (4). Please review bioavailability and bioequivalence data between old and new formulations.

cc:
Orig. NDA #20-058,
HFD-150/Div. File
HFD-150/NChidambaram
HFD-150/EDuffiy
HFD-150/DPease

Entered

ERIC P. Duffy 7/20/00

SIGNATURE OF REQUESTER	METHOD OF DELIVERY *(Check one)*
N. Mumy 07/20/2000	☐ MAIL ☒ HAND
SIGNATURE OF RECEIVER Atiq Rahman 9/27/00	SIGNATURE OF DELIVERER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-058/S-010

JUN 14 2000

Immunex Corporation
51 University Street
Seattle, WA 98101

Attention: Mark W. Gauthier
Senior Manager, Regulatory Affairs

Dear Mr. Gauthier:

We acknowledge receipt of your supplemental application for the following:

Name of Drug: Thioplex (Thiotepa for Injection)

NDA Number: 20-058

Supplement Number: S-010

Date of Supplement: June 08, 2000

Date of Receipt: June 12, 2000

Unless we find the application not acceptable for filing, this application will be filed under Section 505(b)(1) of the Act on August 11, 2000 in accordance with 21 CFR 314.101(a).

All communications concerning this NDA should be addressed as follows:

(if via U.S. Postal Service)

FDA/CDER
Division of Oncology Drug
Products, HFD-150
5600 Fishers Lane
Rockville, Maryland 20857

(if via courier)

FDA/CDER
Division of Oncology Drug Products,
HFD-150
1451 Rockville Pike
Rockville, Maryland 20852

Sincerely,

Dufeel 6-14-00

Dotti Pease
Chief, Project Management Staff
Division of Oncology Drug Products, HFD-150
Office of Drug Evaluation I
Center for Drug Evaluation and Research

cc:
Original NDA 20-058/S-010
HFD-150/Div. Files
HFD-150/CSO/A. Dunson (Peace)

filename: C:\WPWIN61\TEMPLATE\FDA\20058S00.WPD

SUPPLEMENT ACKNOWLEDGMENT